(1)

#1 Appeal Brief (3)

DOCKET NO. : Carle- 3 CIP3 USA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANTS: Ralph A. Nelson, et al.)
SERIAL NO.: 08/833, 096) **EXAMINER:** Jean C. Witz
FILED: April 4, 1997) **ART UNIT:** 1808
TITLE: Bear Derived Isolate and Method)

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner for Patents and Trademarks, Washington, D. C. on: 12/30/98
Jack E. Dominik, Reg. No. 17,620
Name of applicant, assignee, or Registered Rep.

SIGNATURE 12/30/98 DATE

To: Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF TRANSMITTAL LETTER

Dear Sir:

Attached hereto is Appellant's Appeal Brief, filed in triplicate. The Commissioner is hereby authorized to debit the requisite fee under 37 CFR 1.17(f) of $150.00 for filing the Brief in furtherance of the Notice of Appeal filed in this application from Deposit Account No. 04-1308.

The Commissioner is also hereby authorized to credit any overpayments or charge any deficiencies in the payment of fees regarding this Appeal to Deposit Account No. 04-1308.

Respectfully submitted,

DOMINIK, KNECHTEL, DEMEUR & SAMLAN

By: _____
Jack E. Dominik, Reg. No. 17,620
Attorney for Appellants

01/07/1999 SLUANG1 00000027 041308 08833096
01 FC:220 150.00 CH

Miami Corporate Plaza
6175 NW 153rd Street, Suite 225
Miami Lakes, FL 33014
(305) 556-7000 Voice
(305) 556-6577 Fax

DOCKET NO. : Carle- 3 CIP3 USA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANTS: Ralph A. Nelson, et al.)
SERIAL NO.: 08/833, 096)
FILED: April 4, 1997)
TITLE: Bear Derived Isolate and Method)

EXAMINER: Jean C. Witz
ART UNIT: 1808

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Commissioner for Patents and Trademarks, Washington, D.C. on: 12/30/98
Jack E. Dominik, Reg. No. 17,620
Name of applicant, assignee, or Registered Rep.

SIGNATURE 12/30/98 DATE

To: Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is an appeal from the August 4, 1998 final rejection of Claims 1-21, 24-33, 44-5, 49-51, and 63-66 by the Primary Examiner in Group Art Unit 1808.

Jurisdiction of this Appeal resides with the Board of Patent Appeals and Interferences under the provisions of Section 134, Title 35, United States Code, by way of a Notice of Appeal and requisite fee mailed to the United States Patent and Trademark Office with the Certificate of Mailing on October 30, 1998.

TABLE OF CONTENTS

TABLE OF AUTHORITES 3

REAL PARTIES IN INTEREST 4

RELATED APPEALS AND INTERFERENCES 4

STATUS OF CLAIMS 4

STATUS OF AMENDMENTS AFTER FINAL 4

SUMMARY OF THE INVENTION 5

ISSUES 7

GROUPING OF CLAIMS 9

ARGUMENTS 10

I. Claims Drawn To A Pharmacological Composition Comprising 24, 25-dihydroxyvitamin D3 Are Supported By The Disclosure And, Therefore, The Examiner's Rejection Of ThoseClaims Must Be Reversed. 10

II. Applicants Claims Particularly Point Out And Distinctly Claim The Subject Matter Which Applicants Regard As Their Invention And, Therefore, The Examiner's Rejections Must Be Reversed. 12

III. Applicants Claims Are Distinct From One Another And Do Not Contain Double Patenting Issues And, Therefore, The Rejection Must Be Reversed. 16

PRAYER FOR RELIEF 19

APPENDIX A 20

TABLE OF AUTHORITIES

Cases — Page

Hybritech, Inc. v. Monoclonal Antibodies, Inc, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) 10

Andrew Corp. v. Gabriel Elecs., Inc. 847 F. 2d 819, 821, 6 USPQ2d 2010, 2012 (Fed. Cir. 1988) 12

Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 225 USPQ 634, 641 (Fed. Cir. 1985) 12

ZMI Corp. v. Cardiac Resusitator Corp., 844 F. 2d 1576, 6 USPQ2d 1557, 1560 (Fed. Cir. 1988) 14

Mannesmann Demag Corp. v. Engineered Metal Products, Co., 793 Fed. 2d 1279, 1282, 230 USPQ 45, 47 (Fed. Cir. 1986) 14

Inwood Laboratories, Inc. v. Ives Laboratories, 456 U.S. 844, 863 (1982) 16

Carman Indus., Inc. v. Wahl, 724 F.2d 932, 940, 220 USPQ 481, 487 (Fed. Cir. 1983) 17

In Re Vogel, 422 F. 2d 438, 441, 164 USPQ 619, 622 (C. C. P.A. 1970).

Miscellaneous Authority

The American Heritage Dictionary, second college edition, page 1138 . 15

1) **REAL PARTIES IN INTEREST**

Appellants Ralph A. Nelson, Patricia G. Miers, and Kenneth L. Rinehart assert that they are the inventors of the claimed invention and, thus, are the real parties in interest for purposes of standing with this Appeal.

(2) **RELATED APPEALS AND INTERFERENCES**

Appellants state that to the best of their knowledge, no other Appeals or Interferences exist now or in the foreseeable future which will have any bearing on the Board's decision of this Appeal.

(3) **STATUS OF CLAIMS**

Claims 1-66 are currently pending in the case. In a Final Office Action dated August 4, 1998, the Examiner allowed Claims 22, 23, 34-43, 46-48, and 52-62. In that same Office Action, the Examiner finally rejected Claims 1-21, 24-33, 44-5, 49-51, and 63-66. All of the rejected claims are being appealed.

(4) **STATUS OF AMENDMENTS AFTER FINAL**

All amendments to the Claims were entered into the record prior to the final rejection now appealed.

(5) **SUMMARY OF THE INVENTION**

The claimed invention relates to the discovery and isolation of a substance called bear derived isolate ("BDI") produced by fasting and denning black bears. BDI, in combination with various carriers and in various doses, based upon studies conducted with guinea pigs and bone cultures and rats, will likely have beneficial effects on humans in promoting bone growth in those persons having osteoporosis, in conserving nitrogen to a point where hemodialysis in kidney transplants need not be performed in patients with chronic or end stage renal disease, and inhibiting protein breakdown in burn and trauma patients, in permitting long term flights into space by conserving bone calcium and preventing muscular atrophy, in producing weight loss in obese patients in the form of fat reduction while conserving lean body mass, and promoting tranquility in an alert state at normal body temperature.

A related aspect of the invention is directed to the method of the isolation and purification of the bear derived isolate, whether from a fasting bear or a denning bear, to a form where predictable results in the above phenomena are readily achieved alone or in combination with other known metabolic substances. The inventors have also discovered that a fasting or otherwise normal summer bear, as distinguished from a denning bear, will produce the equivalent of a bear derived isolate. Thus, this invention must be considered in terms of a fasting bear, despite the fact that the bulk of the studies have involved denning bears.

BDI and components are found in the serum and urine of denning bears and active bears which are forced to fast. Isolation of BDI requires precipitation of protein from winter urine or serum using methanol; centrifuging the sample and removing precipitated protein as pellets; and drying the BDI into a visible extract.

Further, by the use of thin layer chromatography (TLC), countercurrent chromatography (CCC), and preparative thin layer chromatography (or column chromatography), at least two compounds, both in urine and blood, can be isolated in BDI.

The method of isolation of these compounds permits predictable separation of BDI into the following fractions:

1. Miers-Nelson Component (MNC)
2. Beta-hydroxybutyrate (BHB)

BDI can be divided into three fractions which can be tested for their biologic activity in guinea pigs, rats, and bone culture assays:

Fraction I = BDI-[BHB+MNC] (early fractions),

Fraction II = BHB (middle fractions), AND

Fraction III = MNC (late fractions).

Therefore, it an object of the invention to isolate and evaluate BDI in denning and fasting bears; to isolate BDI in such quantities that it is useful as a treatment; to produce BDI for further research; and, to produce BDI in a form that will permit synthesis in large volumes and at reduces cost.

(6) **ISSUES**

1. The Examiner rejected Claims 63-65 pursuant to 35 U.S.C. sec. 112, first paragraph, taking the position that the specification, while enabling for a composition comprising deproteinated fasting bear serum or urine and the fractions disclosed, does not reasonably provide enablement for a pharmacological composition comprising 24, 25-dihydroxyvitamin D3 or a composition having a molecular weight of 100 or less. Applicants have canceled the Claims relating to molecular weight.

THE ISSUE: Whether Claims drawn to a pharmacological composition comprising 24, 25-dihydroxyvitamin D3 are supported by the Disclosure.

2. The Examiner rejected Claims 1-21, 24-30, 44-45 and 63-66, pursuant to U.S.C. 1112, second paragraph, for varied reasons as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventors regard as the invention.

THE ISSUES: a) Whether use of the phrase "chemistry similar to"in Claims 2, 8, 10, 11, 12, ,15, 17, 18, 19, 24, and 29 is appropriate

b) Whether use of the phrase "ursus-like" in Claims 2, 14, 18, and 21 is appropriate.

c) Whether use of the phrase "resembling the characteristics of a bear derived isolate" in Claim 2 is appropriate.

d) Whether use of the word "comprising" in Claim 1 is appropriate.

e) Whether use of the phrases " at least one vital sign of behavioral modification substance" and " other substances" in Claim 4 is

appropriate.

f) Whether use of the phrase " signature exhibited in the deproteinated isolate of urine or blood" in Claim 13 is appropriate.

g) Whether Claims 1- 15 and 18, Claims 1- 15 and 18 contain inappropriate functional language..

h) Whether use of the word "substance" in Claims 44-45 is appropriate.

3. The Examiner rejected Claims 32- 33, 49, and 51 pursuant to 35 U.S.C § 101 as being substantially duplicative of Claims 31, 48, and 50.

ISSUE: Whether Claims 32, 33, 49, and 51 Claim distinct and patentable subject matter.

7. **GROUPING OF CLAIMS**

Regarding the section 112, first paragraph rejection, Claims 63-65 stand and fall together and are to be considered as one group.

Regarding the section 112, second paragraph, rejection, the following groupings are submitted:

Group 1- concerning use of the phrase "chemistry similar to", Claims 2, 8, 10, 11, 12, ,15, 17, 18, 19, 24, and 29 stand and fall together.

Group 2- concerning use of the phrase "ursus-like", Claims 2, 14, 18, and 21 stand and fall together.

Group 3- concerning use of the phrase "resembling the characteristics of a bear derived isolate", Claim 2 comprises the group.

Group 4- concerning use of the word "comprising" in Claim 1, Claim 1 comprises the group.

Group 5- concerning use of the phrases " at least one vital sign of behavioral modification substance" and " other substances" in Claim 4, Claim 4 comprises the group.

Group 5- concerning use of the phrase " signature exhibited in the deproteinated isolate of urine or blood" in Claim 13, Claim 13 comprises the group.

Group 6- concerning use of supposed functional language in Claims 1- 15 and 18, Claims 1- 15 and 18 comprise the group.

Group 7- concerning use of the word "substance" in Claims 44-45, Claims 44-45 stand and fall together.

8. **ARGUMENTS**

I. Claims Drawn To A Pharmacological Composition Comprising 24, 25-dihydroxyvitamin D3 Are Supported By The Disclosure And, Therefore, The Examiner's Rejection Of Those Claims Must Be Reversed.

The Examiner rejected Claims 63-65 pursuant to 35 U.S.C § 112, first paragraph, arguing that the specification does not reasonably provide enablement for a pharmacologic composition comprising 24,25-dihydroxyvitamin D3 (24,25-D3) or a composition having a molecular weight of 100 or less. As noted above, Applicants have canceled Claim 64 and, therefore, the rejection based on molecular weight is moot.

Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed invention. Enablement is not precluded even if some experimentation is necessary. Hybritech, Inc. v. Monoclonal Antibodies, Inc, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986). Further, a patent does not need teach, and preferably omits, what is well known in the art. Id.

Regarding the Examiner's rejection of Claims drawn to 24,25-D3, the Applicants respectfully submit that the Examiner is in error. As noted in Applicants' May 6, 1998, Amendment in response to the Examiner's January 6, 1998, Office Action, the specification is replete with discussion regarding 24,25-D3 and its pharmacologic properties. More specifically, beginning on page 28, line 8, there is a discussion of the activity of 24,25-D3 entitled Vitamin D and Bone Integrity In the Denning Bear. That section discusses the fact that it is well known that 1,25- dihydroxyvitamin D3 produces, *inter alia*, bone loss. It is further noted that production of 24,25- D3 increases during denning. Until recently, it was

thought that 24,25-D3 had no effect on bone. It is now known that 24,25-D3 aids in preventing bone loss by stimulating bone deposition. It is also known that 24,25-D3 may not be effective when used alone; it may need to be used in conjunction with other substances.

Importantly, beginning on page 46, line 9 and continuing through page 55, line 11 of the disclosure there is a discussion of the Inventors' research which demonstrates that BDI contains 24,25-D3, and that, when removed or withheld from in laboratory studies, results in bone loss.

Beginning on page 46, line 29, and continuing through page 55 line 11, there is a discussion of the bone remodeling capabilities of Bear Derived Isolate (BDI). It is also shown on page 27, beginning at line 20 through page 28, line 26, that BDI contains 24,25- D3. Without BDI, and hence 24,25-D3, ovariectomized mice and guinea pigs show marked bone loss. Those same mice and guinea pigs administered BDI, and again 24,25-D3, show marked bone remodeling.

Applicants Claims are directed specifically to a composition which includes 24,25-D3. This is consistent with the known prior art and Applicants studies which demonstrate that when the 24,25-D3 is removed from the DBI, the bone deposition properties of the BDI diminish.

Regarding the Examiner's reference to the fact that the composition is directed to a pharmaceutical, Applicants are unclear as to what the Examiner meant. Certainly, a pharmaceutical composition is supported by the Disclosure. The primary purpose of the Applicants' invention is directed to pharmaceutical results; a concept well supported by the Disclosure

Thus, Applicants submit that their specification does support a patentable

claim identifying D3 as an active substance which stimulates bone formation. Applicants respectfully request, therefore, that Examiner's rejection be reversed and Applicants' Claims be allowed.

II. Applicants Claims Particularly Point Out And Distinctly Claim The Subject Matter Which Applicants Regard As Their Invention And, Therefore, The Examiner's Rejections Must Be Reversed.

The Examiner rejected 1-21, 24-30, 44-45, and 63-66 under USC § 112, second paragraph, as being definite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner rejected various Claims for a variety of reasons. Each group will be addressed separately below.

a) "Chemistry similar to"

It is well settled that phrases such as "close to", "substantially equal to", and "closely approximate" are ubiquitous terms in patent claims. They will pass the indefinite test if they reasonably describe the claimed invention to those skilled in the arts and distinguish it from the prior art. See, e.g. Andrew Corp. v. Gabriel Elecs., Inc. 847 F. 2d 819, 821, 6 USPQ2d 2010, 2012 (Fed. Cir. 1988). Moreover, it is also well settled that the amount of detail required is dependent on the particular invention and the amount of prior art. See, e.g., Shatterproof Glass Corp. v. Libbey-Owens Ford Co., 758 F.2d 613, 225 USPQ 634, 641 (Fed. Cir. 1985).

Applicants are aware of no prior art known to them nor has the Examiner cited any prior art with reference to their invention. Accordingly, submit that their invention is a pioneer invention and is, therefore is entitled to broad use of

language to claim it.

Applicants further submit that their use of the phrase "chemistry similar to" is sufficient to enable those skilled in the art to practice the invention without undo experimentation. The Disclosure contains throughout its entirety many descriptions as to how the Applicants obtain BDI from the blood and urine of a bear. Beginning on page 20 there is a detailed description of the chemistry involved. Thus, one skilled in the art can easily turn to the Disclosure to get this information. It should also be pointed out that the Applicants use standard isolation, assay, and fractionalization methods in their studies. Once the isolate is derived, the practioner will have the components necessary to practice the invention.

It then follows that considering that since there is no prior art to distinguish the invention from and the current court interpretation regarding literal infringement, that Applicants are entitled to a broad claim. Thus, Applicants claims using the phrase " chemistry similar to" pass the indefinite test. Accordingly, the Examiner's rejection on this group should be reversed.

b) "ursus-like"

The entire Disclosure submitted by Applicants pertains to studies done with bears and more specifically, black bears. It is noted on page 15 of the Disclosure that the genus/species name for the North American Black bear is Ursus americanus. Thus, one wishing to practice the invention need go no further than the Disclosure to obtain the meaning of the word. The Claims themselves further describe the ursus-like substance as having specific properties.

Further, Applicants are entitled to be their own lexicographer when there

is need to coin new expressions to claim an invention. ZMI Corp. v. Cardiac Resusitator Corp., 844 F. 2d 1576, 6 USPQ2d 1557, 1560 (Fed. Cir. 1988). Again, considering the pioneer nature of the invention and the fact that the Applicants have described "Ursus", they are entitled to create and use the phrase "ursus-like" to describe and Claim their invention.

c) "Resembling the characteristics of a bear derived isolate"

Applicants adopt the same argument here as for use of the phrase "chemistry similar to". Further Applicants submit that "bear derived isolate" is described in many locations throughout Applicants' Disclosure.

d) "Comprising"

The Examiner rejected various Claims for including the transitional phrase "comprising". The Examiner specifically states that it is unclear how the word can describe pharmacologic properties. The word comprising as used in patent claims is an open ended word. Mannesmann Demag Corp. v. Engineered Metal Products, Co., 793 Fed. 2d 1279, 1282, 230 USPQ 45, 47 (Fed. Cir. 1986). It is a term of art used to denote inclusion of the claimed elements when an accused infringer adds elements. Id. Applicants are aware of no case law which prevents use of the word when used in reference to a pharmaceutical property of an invention. Applicants use of the word is for the well accepted reason of giving the widest scope of interpretation to the claims.

The word is equivalent to the word "characterized". Id. If the Appeals Board is more comfortable with use of the word characterized, Applicants are amenable to this amendment to their Claims. Indeed, it is the word used by them in their originally submission and was later amended.

e) "At least one vital sign of behavioral modification substance" and "other substances".

Applicants adopt their legal argument as stated for use of the term "chemistry similar to" and "ursus-like". Applicants further state that the Disclosure supports behavioral modification substances. Specifically, on page 30, beginning at line 7, there is a discussion of the "tranquility" effects of BDI. Beginning on line 27 and continuing through page 46 there is discussion of testing done with guinea pigs provided with BDI. The discussion demonstrates the behavioral modification properties of the Claimed composition.

Again, due to the pioneer nature of Applicants' work , support in the law for Applicants lexicography, and support in the Disclosure for such terminology, Applicants submit that the have appropriately claimed their invention.

f) "Signature exhibited in the deproteinated isolate of urine or blood'.

The Examiner rejected Claim 13 stating that the above identified phrase is unclear. In their May 6, 1998, Amendment, Applicants amended Claim 13 to insert the word "marker" after the word"signature. Applicants submit that this amendment more distinctly claims their invention. It is well known in the art that the word "marker" refers to a reliable identifier. The word "signature", as defined in The American Heritage Dictionary, second college edition, page 1138, means, *inter alia*, "[a] distinctive mark, characteristic, or name."

Applicants submit that the key to Claim 13 is a deproteinated isolate which exhibits an ability to cause tranquility, reduction in body temperature, or heart rate. The compound must include the signature BDI in order to produce such effects. Thus, the isolate does have a "signature" which can be identified as BDI ("the

marker").

g) "Functional Language".

Applicants are unclear as to what the Examiner is referring in this rejection. The claimed invention in each of the relevant claims refers to a pharmacologic composition or substance having various properties, those properties resulting in a desired effect. It is impossible to claim a composition directed to a desired effect without describing the effect. Applicants maintain, therefore, that their Claims are appropriate. Moreover functionality is the hallmark of utility patents. See, e.g., Inwood Laboratories, Inc. v. Ives Laboratories, 456 U.S. 844, 863 (1982).

Applicants submit that their claims are properly crafted in this regard. If Applicants misunderstand the Examiner's rejection, help in this regard is appreciated.

h) "Substance"

Applicants submit that there is a typographical error in Claims 44 and 45. In their May 6, 1998 Amendment, they changed substance to compound in line 2 of Claim 44 and line 3 of Claim 45 but neglected to do so in lines 3 and 4, respectively. Applicants request that they be allowed to amend the Claims so that they consistently refer to "compound.

III. Applicants Claims Are Distinct From One Another And Do Not Contain Double Patenting Issues And, Therefore, The Rejection Must Be Reversed.

Double patenting carries a heavy burden of proof on the one seeking to prove it. Carman Indus., Inc. v. Wahl, 724 F.2d 932, 940, 220 USPQ 481, 487 (Fed. Cir. 1983). The test for double patenting is whether one of the Claims could be literally infringed without literally infringing the other Claim. In Re Vogel, 422

F. 2d 438, 441, 164 USPQ 619, 622 (C. C. P.A. 1970). Applicants submit that the Examiner cannot meet her burden of proof on double patenting.

The Examiner rejected Claims 32 and 33 arguing that they are substantially duplicative of claim 31. Applicants respectfully disagree. Claim 31 is directed to a multitude of effects in *guinea pigs* injected with the composition. Applicants submit that if the composition of matter of Claim 31 is administered, either increased osteoblastic activity, decreased osteoclastic activity, or a combination of both may occur. Increased osteoblastic activity with corresponding increased osteoclastic activity may not result in enhanced bone remodeling. Likewise, decreased osteoclastic activity without increased osteoblastic activity will not result in enhanced bone remodeling. Finally, a combination of increased osteoblastic activity and decreased osteoclastic activity may result in enhanced bone remodeling only if the original levels were normal to begin with.

Applicants further submit that the claim 33 is directed to an ovariectomized rat in which administration of the composition of matter causes enhanced bone formation. As evidenced by the Specification examples, guinea pigs and rats reacted differently, albeit positively, to administration of the composition of matter. Applicants respectfully submit, therefore, that claims 32 and 33 are properly drawn and distinct claims.

The Examiner also rejected claim 49 on double patent on grounds arguing that it is duplicative of claim 48. Again, Applicants respectfully disagree. Claim 48 is directed to a composition of matter obtained from a *fasting* black bear from which all food has been withheld for *two weeks or more*. Claim 49, on the other hand, is directed to a *denning* black bear which voluntarily neither eats, drinks,

urinates, or defecates for lengthy periods of time. Applicants submit that a fasting bear may drink, urinate, and defecate. Further, the "lengthy period of time" identified in claim 49 can exceed the two week limitation of claim 48. Applicants respectfully submit, therefore, that claim 49 contains distinctly patentable subject matter from claim 48.

Finally, the Examiner rejected claim 50 under double patenting ground arguing that it is duplicative of claim 51. Again, Applicants respectfully disagree. Both Claims 50 and 51 are dependant claims of independent claim 49. Claim 50 is directed to a composition of matter objected to "in vitro" analysis while claim 51 is a composition of matter subjected to "in vivo analysis with ovariectomized rats". Applicants first submit that there is a significant distinction between in vitro and in vivo analysis. Applicants further submit that the in vivo analysis with ovariectomized rats does not show the increased fibroblastic activity of the in vitro analysis of claim 50. Applicants submit, therefore, that claim 51 contains patentable subject matter distinct from that of claim 50.

PRAYER FOR RELIEF

Appellants submit that the Claims, as amended, are proper and supported by the Specification. Appellants respectfully request that this Honorable Board, therefore, reverse the Examiner and order that a Notice of Allowance be issued in this case.

Respectfully submitted,

DOMINIK, KNECHTEL, DEMEUR & SAMLAN

By: _____
Jack E. Dominik, Reg. No. 17,620
Attorney for Appellants

Miami Lakes Corporate Plaza
6175 NW 153rd Street, Suite 225
Miami Lakes, FL 33014
(305) 556-7000 Voice
(305) 556-6577 Fax

APPENDIX A

1. A composition of matter comprising pharmacological properties and which is a deproteinated isolate which has been obtained from a sample of urine or serum taken from a fasting bear from which food has been withheld for two weeks or more, which sample has been subjected to deproteination, then the deproteinated isolate having the pharmacological properties of inducing, when injected into another mammal, conditions observable in denning black bears including reduced heart rate, temperature reduction, or a tranquility distinguishable from normal behavior.

2. An ursus-like pharmacological composition of matter comprising chemistry similar to a bear derived isolate obtained from the blood or urine of a fasting bear, which fasting bear has not eaten for two weeks or more, which alone or in combination with other metabolites, when injected into a mammal other than a bear, produces at least one of the phenomena as exhibited by a denning black bear selected from the group comprising reduced heart rate, reduced body temperature, or a tranquility distinguishable from normal behavior.

3. The composition of matter of claim 2, in which said mammal is a guinea pig.

4. A pharmacological composition of matter comprising evidence of at least one vital sign of behavioral modification substance present in the blood or urine of fasting bears, which fasting bears have not eaten for two weeks or more, said composition when administered alone or in combination with metabolites, when injected into a mammal other than a bear, produces reduced vital signs in said mammal.

5. The composition of claim 4, in which the mammal is a guinea pig.

6. The composition of claim 4, alone or in combination with metabolites, in which the reduced vital sign is reduced temperature.

7. The composition of matter of claim 4, alone or in combination with metabolites, in which said reduced vital sign is reduced pulse rate.

8. A composition of matter comprising chemistry similar to an isolate of whole blood or whole urine sample taken from a fasting black bear, which fasting bear has not eaten for two weeks or more, which sample has been deproteinated to form the isolate composition which, when added to a carrier and injected into a mammal other than a black bear, produces any of the following conditions in said mammal:

a) reduced heart rate;

b) reduced temperature; or

c) wakeful tranquility.

9. The composition of matter of claim 8, in which said mammal is a guinea pig.

10. A composition of matter comprising chemistry similar to the deproteinated urine or blood serum isolate of fasting bear, which bear has not eaten for two weeks or more, which, when administered to a mammal other than a denning black bear, produces improved bone remodeling.

11. An anti-osteoclastic pharmaceutical composition of matter comprising chemistry similar to the deproteinated urine or blood serum isolate of fasting bear which bear has not eaten for two weeks or more, which, when administered to a mammal other than a denning black bear, exhibits overall enhanced bone formation whether by enhanced osteoblastic activity, or diminished osteoclastic activity, or enhanced fibroblastic activity, or any positive combination of the foregoing, wherein the net result is enhanced bone remodeling.

12. A pharmacological compound comprising chemistry similar to a sample of whole blood or whole urine taken from a fasting black bear which fasting bear has not eaten for two weeks or more, which has been deproteinated; said deproteinated sample then being purified, isolated, or concentrated to the point which renders said sample, when injected into a mammal other than a bear, capable of eliciting a response of a denning black bear in mammals which do not den, said response including stimulating bone mass production; or increasing the recycling of urea, thus combating uremia dn preserving body protein; or inhibiting muscular wasting.

13. A pharmacological compound comprising a signature marker exhibited in the deproteinated isolate of urine or blood of a fasting bear which bear has not eaten for two weeks or more, alone or in combination with metabolites, which isolate, when injected in a mammal other than a bear, produces tranquility in which said mammal remains calm but alert with a decrease in metabolism including reductions in body temperature or heart rate.

14. An ursus-like pharmacological compound comprising the deproteinated isolate of the urine or blood of a fasting bear which, when injected into a mammal other than a bear, produces phenomena as exhibited in a denning black bear which bear neither eats, drinks, urinates, nor defecates for lengthy periods of time, said phenomena including stimulation of bone production in mammals, including humans, at risk to develop osteoporosis, regeneration of protein from nitrogenous waste products at a rate faster than protein breakdown, and producing anorexia.

15. A pharmacological compound comprising chemistry similar to a fraction of the aqueous portion of blood or urine taken from a fasting bear which has not eaten for two weeks or more, which can be used in the group of phenomena comprising treatment of osteoporosis, chronic renal failure, burns and trauma, loss of muscle mass and eating disorders such as obesity; or allowing safe long term space flights by maintaining bone and muscle mass in astronauts.

16. A method for obtaining an isolate form the blood or urine of a fasting bear which bear has not eaten for two weeks or more, such isolate being sufficiently free of impurities for repeated administration to mammals to induce activity of a kind observed in denning bears comprising the steps of:

- drawing a sample of blood or urine from said bear,
- deproteinating and extracting the isolate from such sample with organic solvents,
- further purifying the presence of said isolate by countercurrent chromatography, flash column chromatography, preparative thin layer chromatography, and/or high performance liquid chromatography, and
- testing the purity of the isolate so obtained by TLC and/or chemical or spectroscopic detection.

17. An isolate, comprising chemistry similar to an isolate obtained from a sample of the urine of a fasting bear, which bear has not eaten for two weeks or more, such isolate being derived by:

- first deproteinating the sample,
- second, further separating the sample chromatographically into fractions, and then
- third, testing the fractions for a purity of isolation which permits the isolate when administered to a mammal other than a bear to induce behavioral characteristics of denning.

18. A composition of matter comprising an ursus-like pharmacological isolate comprising chemistry similar to a urine sample concentrate taken from a fasting bear, which bear has not eaten for two weeks or more, which urine sample concentrate remains after deproteinating such sample and thereafter purifying the same by chromatographic treatment.

19. A pharmacological composition of matter comprising chemistry similar to a concentrate of a deproteinized sample of whole urine or blood taken from a fasting bear, which bear has not eaten for two weeks or more having the following properties:

- soluble in water, methanol, and 1-butanol,
- insoluble in less polar organic solvents including ethyl acetate, chloroform, toluene and hexane,
- stable at room temperature for four days or more,
- heat resistant to 65°C, and
- stores well when frozen in a light resistant container under nitrogen gas.

20. The pharmacological composition of matter as set forth in claim 19 above which gives a pink spot with ninhydrin at an R_f value of 0.74 to 0.80 on a silica plate with 1-butanol:acetic acid:water (4:1:1).

21. An ursus-like pharmacological composition of matter comprising the following characteristics:

- soluble in water, methanol, and 1-butanol,
- insoluble in less polar organic solvents including ethyl acetate, chloroform, toluene, and hexane,
- stable at room temperature for four days or more,
- heat resistant to 65°C, and
- stores well when frozen in a light resistant container under nitrogen gas,
- which composition of matter has been obtained from deproteinating the urine or blood of a fasting bear which has not eaten for two weeks or more and
- which, when injected in a guinea pig, produces some of the same phenomena observable in a fasting bear, such as heart rate, reduced temperature, or wakeful tranquility.

24. A composition of matter comprising chemistry similar to a deproteinated urine or serum of a fasting bear, which bear has not eaten for two weeks or more, which composition has the following property:

- soluble in water, methanol, and 1-butanol.

25. The composition of claim 24 including the following property:

- insoluble in less polar organic solvents including ethyl acetate, chloroform, toluene and hexane.

26. The composition of claim 24 with the following property:

- stable at room temperature for four days or more.

27. The composition of claim 24 with the following property:

- heat resistant to 65° C.

28. The composition of claim 35 having the following characteristic:

- stores well when frozen in a light-resistant container under nitrogen gas.

29. A composition of matter comprising chemistry similar to deproteinated urine or serum of a fasting bear, which bear has not eaten for two weeks or more, having the following properties:

- soluble in water, methanol, and 1-butanol,
- insoluble in less polar organic solvents including ethyl acetate, chloroform, toluene, and hexane,
- stable at room temperature for four days or more,
- heat resistant to 65°C, and
- stores well when frozen in a light resistant container under nitrogen gas.

30. A deproteinated urine or serum of a fasting bear which has not eaten for two weeks or more comprising a therapeutic compound producing, in any combination, the following behavior in another mammal:

- tranquility, or
- reduced heart rate, or
- increased osteoblastic activity, or
- decreased osteoclastic activity.

31. A composition of matter having the characteristics of deproteinated urine or serum of a fasting bear, which bear has not eaten for two weeks or more and capable of producing the following behavior in a guinea pig injected with said composition produces the following:

- tranquility, or
- reduced heart rate, or
- increased osteoblastic activity, or
- decreased osteoclastic activity.

32. A composition of matter having the characteristics of deproteinated urine or serum of a fasting bear, which bear has not eaten for two weeks or more and capable of producing when injected in a guinea pig:

- enhanced bone remodeling.

33. A composition of matter having the characteristics of deproteinated urine or serum of a fasting bear, which bear has not eaten for two weeks or more and capable of producing when injected in an ovariectomized rat:

- enhanced bone formation.

44. A composition functioning to reduce osteoblastic alkaline phosphatase comprising at least one compound extracted from the serum or urine of a fasting bear, said at least one substance being capable of functioning as an inhibitor of osteoblastic activity as shown by diminution of alkaline phosphatase production.

45. A composition functioning to reduce osteoclast as demonstrated by reduction in production of tartrate resistant acid phosphatase comprising at least one compound extricated form the serum or urine of a fasting bear, said at least one substance being capable of functioning as an inhibitor of osteoclastic activity as shown by diminution of tartrate resistant acid phosphatase.

49. A composition of matter comprising the deproteinated urine or serum of a denning black bear, which denning black bear neither eats, drinks, urinates, or defecates for lengthy periods of time having the following properties:

- soluble in water, methanol, and 1-butanol,
- insoluble in less polar organic solvents including ethyl acetate, chloroform, toluene, and hexane,
- stable at room temperature for four days or more,
- heat resistant to 65°C, and
- stable when frozen in a light resistant container under nitrogen gas

which, when injected into a guinea pig, is capable of producing reduced heart rate, reduced temperature, or observable tranquility differing from normal.

50. The composition of matter of claim 49 which, when subjected to *in vitro* analysis, produces the following:

- increased osteoblastic activity, or
- decreased osteoclastic activity, or
- increased fibroblastic activity.

51. The composition of matter of claim 49 which, when subjected to *in vitro* analysis with ovariectomized rats, produces the following:

- increased osteoblastic activity,
- decreased osteoclastic activity, or
- both.

63. A pharmacological composition of matter comprising the capability of enhancing bone formation in ovariectomized rats taken from a substance present in the blood or urine of fasting bears, which when fasting are unique in that they have not eaten for two weeks or more, said composition including a quantity of resorptive form of 24,25-dihydroxyvitamin D_3 which stimulates bone formation.

65. In the pharmacological composition of matter of claim 64, said composition being characterized by an operative an effective quantity of 24,25-dihydroxyvitamin D_3.

66. The method of producing a pharmaceutical composition from the blood or urine of a fasting bear, which bear has not eaten for two weeks or more, comprising the steps of:

- harvesting the blood or urine from said bear,
- using counter current chromatography (CCC) to divide the thus withdrawn composition from the bear into 10 factions; and isolating the inhibitors of bone formulation in Fractions I, II, and III, and purifying the Fractions V, VI, and VII that contain potent stimulation of bone formation, both in the stimulation and proliferation of osteoblast and fibroblasts as well as containing inhibitors to osteoclastic formation and direct inhibitors of resorption by osteoclast.

A:\CARLEAPP.BRE